FEV1 is a stronger mortality predictor than FVC in mild-to-moderate patients with COPD and an increased risk for cardiovascular disease

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ORIGINAL RESEARCH

FEV_1 is a stronger mortality predictor than FVC in patients with moderate COPD and with an increased risk for cardiovascular disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. Impaired lung function is associated with heightened risk for death, cardiovascular events, and COPD exacerbations. However, it is unclear if forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) differ in predictive value.

Patients and Methods: Data from 16,485 participants in the Study to Understand Mortality and Morbidity (SUMMIT) in COPD were analyzed. Patients were grouped into quintiles for each lung function parameter (FEV_1 %predicted, FVC %predicted, FEV_1/FVC). The four highest quintiles (Q2–Q5) were compared to the lowest (Q1) to assess their relationship with all-cause mortality, cardiovascular events, and moderate-to-severe and severe exacerbations. Cox-regression was used, adjusted for age, sex, ethnicity, body-mass index, smoking status, previous exacerbations, cardiovascular disease, treatment, and modified Medical Research Council dyspnea score.

Results: Compared to Q1 (<53.5% FEV_1 predicted), increasing FEV_1 quintiles (Q2 53.5–457.5% predicted, Q3 57.5–461.6% predicted, Q4 61.6–465.8% predicted, and Q5 ≥65.8%) were all associated with significantly decreased all-cause mortality (20% (4–34%), 28% (13–40%), 23% (7–36%), and 30% (15–42%) risk reduction, respectively). In contrast, a significant risk reduction (21% (4–35%)) was seen only between Q1 and Q5 quintiles of FVC. Neither FEV_1 nor FVC was associated with cardiovascular risk. Increased FEV_1 and FEV_1/FVC quintiles were also associated with the reduction of moderate-to-severe and severe exacerbations while, surprisingly, the highest FVC quintile was related to the heightened exacerbation risk (28% (8–52%) risk increase).

Conclusion: Our results suggest that FEV_1 is a stronger predictor for all-cause mortality than FVC in moderate COPD patients with heightened cardiovascular risk and that subjects with moderate COPD have very different risks.

Keywords: airflow limitation, cardiovascular risk, exacerbation, lung function, lung volumes, death rate

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, progressive disorder of the airways and lung parenchyma and is the fourth leading cause of death.[1] Clinical variables that predict mortality are important for identifying patients at highest risk and include lung function, exacerbation burden and comorbidities.[1–4] Interestingly, when comparing mortality risk based purely on lung function and the symptoms-exacerbation risk-based Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 COPD classification, lung function served as a better predictor.[5]

It has long been debated whether forced expiratory volume in one second (FEV_1) or forced vital capacity (FVC) is the best physiological prognostic measure and if the relationship between FEV_1 and mortality is due to airflow limitation or low lung volumes. Analyzing the 7489 participants in the general population in the Atherosclerosis Risk in Communities study, Burney & Hooper concluded that the overall mortality was more strongly related to FVC than to FEV_1;[6] this was supported by a post hoc analysis of the Burden of Obstructive Lung Disease study reporting that the national COPD related mortality was more strongly associated with the prevalence of spirometric restriction than obstruction.[7] In contrast, other analyses, such as the Normative Aging Study concluded that FEV_1 is more strongly related to mortality than FVC in a general population.[8]

Cardiovascular disease (CVD) frequently accompanies COPD.[9,10] The close relationship is due to common etiologies (i.e., aging, smoking), increased systemic inflammation, hypoxemia, and increased pulmonary vascular resistance.[10] The interplay between CVD and COPD increases the morbidity and mortality of each disorder. For instance, it has been shown that coronary artery calcification, a non-invasive marker for coronary artery disease is associated with increased mortality in COPD.[11] However, it is debated if established CVD is an independent risk factor for COPD exacerbations.[12,13] Regarding cardiovascular mortality, a strong association has been found with FVC,[14] FEV_1,[15–17] and the rate of lung function decline[18] in population-based studies, suggesting that cardiovascular morbidity may be a relevant factor when investigating the relationship between lung function and mortality. Finally, COPD exacerbations pose an increased risk for cardiovascular events.[19,20]

Given the contrasting findings illustrated above, and the need to risk stratify COPD patients with comorbid CVD, we aimed to examine the prognostic value of the spirometric indices by analyzing the data of the Study to Understand Mortality and Morbidity in COPD (SUMMIT) trial.

Patients and Methods

Study Design and Participants

The SUMMIT was a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial assessing the effect of once-daily treatment with fluticasone furoate/vilanterol (100/25 μg), fluticasone furoate (100 μg), vilanterol (25 μg), or matched placebo on mortality in patients with moderate COPD; i.e., FEV_1 between 50% and 70% of predicted value, and an increased cardiovascular risk.[21] For patients ≥40 years of age, this was defined as any one of the following: established coronary artery disease, established peripheral vascular disease, previous stroke, previous myocardial infarction, or diabetes mellitus with target organ disease. In addition, for patients ≥60 years of age, any one of the criteria applicable for patients ≥40 years of age or two of the following: being treated for hypercholesterolemia, being treated for hypertension, being treated for diabetes mellitus, or being treated for peripheral vascular disease.[21] The event-driven study included 16,485 participants and lasted until at least 1000 deaths were recorded. There was no difference between the four treatment arms for the primary outcome of all-cause mortality.[22]

In this post hoc analysis of the SUMMIT study population, we hypothesized that FVC may be a better predictor of overall mortality and major cardiovascular events than FEV_1 and FEV_1/FVC, whereas FEV_1 and FEV_1/FVC would be stronger predictors of COPD exacerbations than FVC.

Major cardiovascular events included cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack. We analyzed moderate to severe and severe exacerbations separately. A moderate COPD exacerbation was defined as an exacerbation treated with antibiotics and/or systemic corticosteroids whereas a severe COPD exacerbation required hospitalization.

All participants in the current analysis provided written, informed consent for trial participation. The study was conducted at 1373 sites in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by local ethics committees (Supplement 1). Trial registration number: NCT01313676.

Lung Function Measurements

Post-bronchodilator spirometry has been performed according to the European Respiratory Society/American Thoracic Society guidelines.[23] Prior to the spirometry long-acting β-agonists and inhaled corticosteroids were withheld for 48 hours, long-acting muscarinic antagonists were withheld for 1 week. Patients with systemic steroid use within 30 days were not included. Lung function measurements at screening were repeated after a 4–10 days run-in period at the baseline visit.

Statistical Analyses

For each measure (percent predicted FEV_1, percent predicted FVC and FEV_1/FVC ratio), participants were allocated into lung function quintiles (Table 1). The number of volunteers allocated in each quintile was compared between the screening and baseline visit.

For primary analyses, lung function data at screening were analyzed. Cox proportional hazards models were applied, adjusted for age, sex, ethnicity, body mass index (BMI), smoking status, previous COPD exacerbations, cardiovascular entry criteria, ischemic and vascular disease indicators, treatment, and modified Medical Research Council (mMRC) dyspnea score. For each outcome, the lowest quintile (Q1) for each lung function measure was used as the reference. Data are expressed as median (95% confidence interval).

Results

Distribution of Lung Function Data

In total, data of 16,485 participants of the intent-to-treat analysis were investigated. Lung function data both at screening and baseline were grouped into quintiles. When comparing the number of patients allocated to each quintile at screening and baseline (at randomization), respectively, only 44%, 54%, and 54% of participants were grouped in the same FEV_1, FVC, and FEV_1/FVC quintiles, illustrating the variability in these spirometric indices (Table 2).

FEV_1, FVC, and FEV_1/FVC as Predictors for All-Cause Mortality, Cardiovascular Events, and COPD Exacerbations

Compared with patients with the lowest FEV_1 (Q1, <53.5% predicted), each of the higher quintiles was associated with better survival, ranging from a 20% lower risk in Q2 to a 30% lower risk in Q5 (Table 1, Figure 1). Although there was a trend for decreasing mortality along the increasing quintiles of FEV_1/FVC (7.8%, 6.7%, 5.9%, 5.4%, and 5.9%, from Q1 to Q5), this did not reach the level of significance. In contrast, for FVC only mortality in quintile 5 (FVC≥87.6% predicted) differed significantly from that of quintile 1 (FVC<67.4% predicted). No lung function indices were predictive of a major cardiovascular event.

Table 1 Association Between Lung Function Indices and Time to Mortality, Cardiovascular Events, Moderate and Severe Exacerbations, and Severe Exacerbations

		Time to Death Risk Reduction vs. Q1	Time to First Major Cardiovascular Event Risk Reduction vs. Q1	Time to First Moderate/ Severe Exacerbation Risk Reduction vs. Q1	Time to First Severe Exacerbation Risk Reduction vs. Q1
FEV_1% Predicted	Q1 <53.5%				
	Q2 53.5 to 57.5%	**20% (4 to 34%)**	5% (−20 to 25%)	**11% (3 to 19%)**	10% (−5 to 23%)
	Q3 57.5 to 61.6%	**28% (13 to 40%)**	15% (−8 to 33%)	**15% (7 to 22%)**	**25% (12 to 37%)**
	Q4 61.6 to 65.8	**23% (7 to 36%)**	9% (−15 to 28%)	**23% (16 to 30%)**	**37% (25 to 47%)**
	Q5 ≥65.8%	**30% (15 to 42%)**	7% (−18 to 26%)	**27% (20 to 33%)**	**40% (28 to 49%)**
FVC % Predicted	Q1 <67.4%				
	Q2 67.4 to 73.6%	14% (−4 to 29%)	16% (−7 to 34%)	2% (−8 to 10%)	4% (−15 to 20%)
	Q3 73.6 to 79.5%	11% (−8 to 27%)	−4% (−30 to 17%)	−4% (−14 to 5%)	0% (−20 to 17%)
	Q4 79.5 to 87.6%	14% (−4 to 29%)	11% (−13 to 29%)	−6% (−17 to 3%)	−13% (−34 to 6%)
	Q5 ≥87.6%	**21% (4 to 35%)**	21% (−1 to 38%)	**−22% (−34 to −11%)**	**−28% (−52 to −8%)**
FEV_1/FVC	Q1 <0.51				
	Q2 0.51 to 0.57	0% (−21 to 16%)	−7% (−36 to 16%)	**18% (11 to 25%)**	**22% (9 to 33%)**
	Q3 0.57 to 0.62	7% (−12 to 24%)	−8% (−38 to 15%)	**28% (22 to 35%)**	**39% (28 to 49%)**
	Q4 0.62 to 0.66	10% (−10 to 26%)	−12% (−43 to 12%)	**29% (22 to 35%)**	**41% (29 to 50%)**
	Q5 ≥0.66	−5% (−28 to 14%)	−18% (−50 to 8%)	**36% (30 to 42%)**	**48% (37 to 57%)**

Notes: Results are from Cox Proportional Hazard models and are presented as risk reduction compared with Q1 quintile groups (with 95% confidence intervals). These are calculated as (1–hazard ratio) × 100. Negative % reductions indicate increase in risk, i.e., hazard ratio >1. Nominally significant differences are presented in bold ($p<0.05$, no adjustment for multiplicity).

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 2 Distribution of Participants in Lung Function Quintiles at Screening and Baseline

	FEV_1	Screening				
		Q1: <53.5% (N=3296)	**Q2: ≥53.5 to <57.5% (N=3297)**	**Q3: ≥57.5 to <61.6% (N=3297)**	**Q4: ≥61.6 to <65.6% (N=3297)**	**Q5: ≥65.6% (N=3296)**
BASELINE	Q1: <52.3% (N=3296)	1844	858	350	178	65
	Q2: ≥52.3 to <56.7% (N=3297)	941	1167	741	311	137
	Q3: ≥56.7 to <61.1% (N=3297)	319	808	1109	732	329
	Q4: ≥61.1 to <66.0% (N=3297)	119	308	743	1235	892
	Q5: ≥66.0% (N=3297)	73	156	354	841	1873
	FVC	**Q1: <67.4% (N=3296)**	**Q2: ≥67.4 to <73.6% (N=3297)**	**Q3: ≥73.6 to <79.5% (N=3297)**	**Q4: ≥79.5 to <87.6% (N=3297)**	**Q5: ≥87.6% (N=3297)**
	Q1: <52.3% (N=3296)	2173	702	264	113	44
	Q2: ≥65.9 to <72.6% (N=3297)	798	1412	739	266	82
	Q3: ≥72.6 to <78.8% (N=3297)	224	856	1357	690	170
	Q4: ≥78.8 to <87.2% (N=3297)	68	272	773	1548	635
	Q5: ≥87.2% (N=3297)	33	55	164	680	2365
	FEV_1/FVC	**Q1: <0.51 (N=3296)**	**Q2: ≥0.51 to <0.57 (N=3297)**	**Q3: ≥0.57 to <0.62 (N=3297)**	**Q4: ≥0.62 to <0.66 (N=3296)**	**Q5: ≥0.66 (N=3297)**
	Q1: <0.51 (N=3296)	2480	610	122	37	33
	Q2: ≥0.51 to <0.57 (N=3297)	609	1668	720	196	90
	Q3: ≥0.57 to <0.62 (N=3297)	112	718	1428	757	269
	Q4: ≥0.62 to <0.66 (N=3296)	52	181	716	1407	955
	Q5: ≥0.66 (N=3297)	33	103	296	888	1935

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Compared with quintile 1, higher FEV_1 and FEV_1/FVC quintiles were all associated with a reduction of risk of moderate-to-severe and severe exacerbations (Table 1). Unexpectedly, quintile 5 of FVC showed an increased risk of a moderate-to-severe and severe exacerbation compared to quintile 1. Despite analyzing FEV_1 within a narrow range (50–70%), there was a strong association between FEV_1 and exacerbation risk, with the lowest FEV_1 quintile having a 27% higher risk of moderate/severe exacerbations compared with the highest FEV_1 quintile (≥65.8%), and a 40% increase for severe exacerbations.

Discussion

Analyzing the results of the SUMMIT trial, we found that FEV_1 was a better predictor for mortality and exacerbation risk than FVC, while neither of them was associated with the risk for major cardiovascular events. The clearer relationship between mortality and FEV_1 than with FVC suggests that airflow limitation, rather than lung volume, predicts mortality in patients with COPD and heightened cardiovascular risk.

Previous general population studies highlighted the predictive role of FVC versus FEV_1.[6,14] There are possible explanations for the discrepancies. First, the current study included only patients with an obstructive lung function pattern.[21] A restrictive pattern may also be common in the general population and associated with poverty[7] and morbid obesity, which may both lead to increased mortality.[24] Although our analysis was adjusted for BMI, socioeconomic data were unavailable and several other variables,

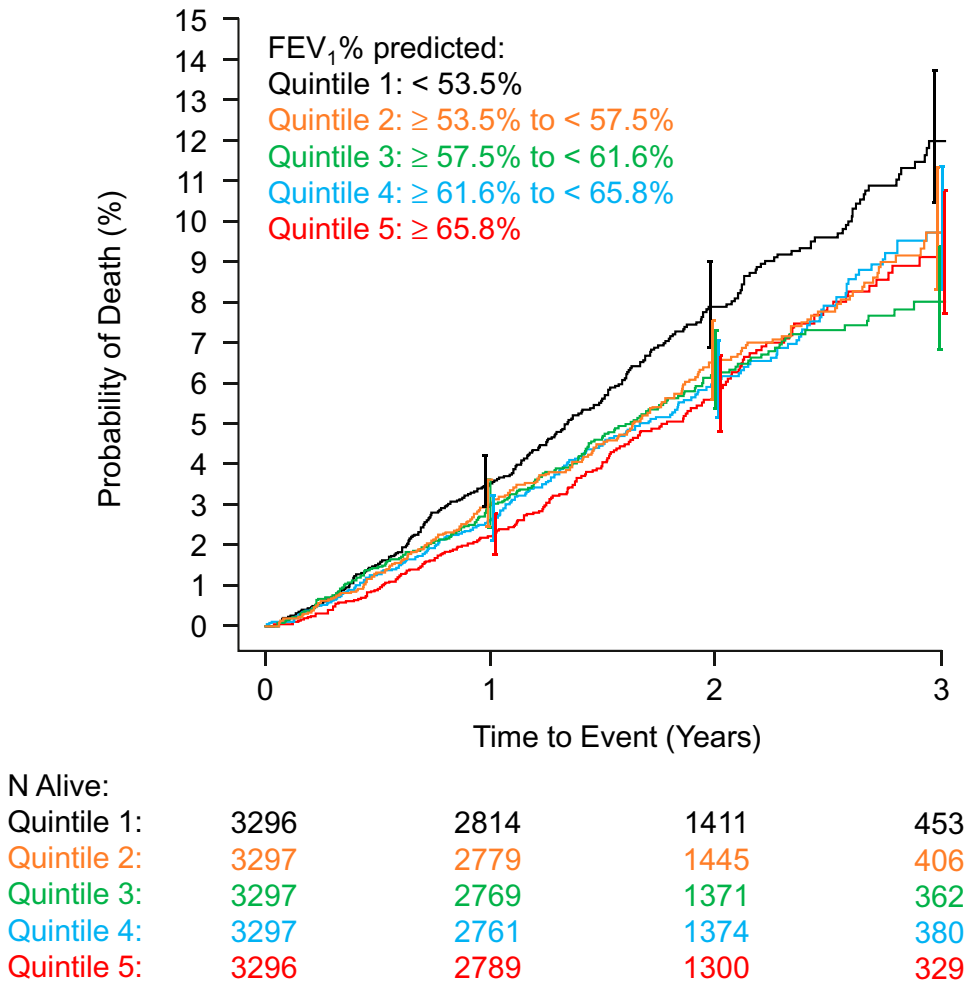

Figure 1 Kaplan–Meier plot showing unadjusted relationship between FEV_1% predicted at screening and all-cause mortality.
Abbreviations: FEV_1, forced expiratory volume in one second; N, number of patients.

such as very severe heart failure (which may lead to reduced FVC), were not included, which may have influenced our findings. While inclusion into SUMMIT was not restricted by FVC as it was for FEV_1, we only included patients with moderate COPD, which imposed some restrictions on FVC indirectly. In this sense, the previously seen association between reduced lung volumes and cardiovascular outcomes may have been driven by subjects with very low FVC.[14]

We found a steep gradient between FEV_1 quintiles and exacerbation risk. As the FEV_1 cut-off value generally applied for separating moderate from severe COPD is quite arbitrary, our findings add to the increasing perception that, for usual clinical care, these arbitrary FEV_1 cut-off values hold little clinical value.

Our article also highlights the obscurity of lung function values from a single spirometry. Only approximately half of the participants allocated to different lung function quintiles at screening were grouped in the same quintile at baseline. Indeed, approximately 1% of patients changed from the lowest to highest quintiles or vice versa. This can be likely explained by the methodological variability of lung function measurements and physiological variability of the airway caliber.

Our analysis has limitations. Only patients with moderate COPD were included and a wider lung function range would likely have provided more robust data. Lung function aside, hypoxia, hypercapnia, BMI, dyspnea, and exercise capacity are also strong predictors of mortality in COPD.[1] Although our analyses were adjusted for BMI and mMRC dyspnea score, blood gas values and exercise capacity test were not available in SUMMIT. However, patients on long-term oxygen were excluded, as were those with very severe heart failure, severe renal failure,

or whose life expectancy from diseases other than vascular disease and COPD was under 3 years. We therefore do not believe that our findings are the result of confounding by these other risk factors.

Confirming previous findings, lower FEV_1 and FEV_1 /FVC were associated with higher risk for COPD exacerbations.[13,25,26] Increased disease severity is associated with heightened airway and systemic inflammation.[27] The ECLIPSE study highlighted the potential role of persistent systemic inflammation leading to frequent exacerbations.[28] However, analyzing the SUMMIT data, the levels of systemic inflammatory biomarkers did not relate to the frequency of flare-ups.[29] Interestingly we found that the highest FVC quintile was associated with an increased exacerbation risk. This, together with the gradually increased risk for exacerbation with FEV_1 decline suggest that more severe emphysema may be related to higher number of exacerbations. This is in line with the ECLIPSE study;[25] however, no computed tomography was performed in the SUMMIT trial. Our results are similar to the findings of the TIOSPIR study showing that larger FVC was associated with increased exacerbation risk.[12]

Conclusion

In conclusion, we found strong relationships between FEV_1 and exacerbation rate and all-cause mortality, but not with major cardiovascular events, in SUMMIT. These were stronger than for FVC and stronger than we anticipated for patients with moderate COPD and a limited FEV_1 range.

Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; SUMMIT, Study to Understand Mortality and Morbidity.

Data Sharing

The authors confirm that they intend to share individual deidentified participant data, including demographics, comorbidities, mortality, lung function, and treatment. In addition, other study-related documents will be made available, including raw dataset, analysis ready dataset, reporting and analysis plan, clinical study report, case report forms, and protocol.

It is GSK policy to provide access to patient-level data within 6 months of publishing the results of the primary endpoints of the study. Researchers can enquire about the availability of data from GSK clinical studies that are not listed on www.clinicalstudydatarequest.com before they submit a research proposal. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via www.clinicalstudydatarequest.com.

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